REMARKS

I. Status of Claims

Claims 1-30 are pending and stand rejected under 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under 35 U.S.C. §102(b)

A. Esmon *et al.*

Claims 1, 4-8 and 17-30 stand rejected as lacking novelty over Esmon, in view of Kurosawa *et al.* (1997; 1998). According to the examiner, Esmon discloses that hurudin, a specific thrombin inhibitor, blocked thrombin mediated increases in circulating EPCR. Moreover, the examiner points to the following passage:

> Based on the vascular location of EPCR on large vessels and the apparent thrombin-mediated shedding, it would appear that monitoring plasma EPCR levels might provide an indication of large vessel disease activity associated with thrombin generation. This could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these patients.

Esmon at page 255. From this, it is concluded that the reference adequately discloses the use of sEPCR assays to monitor the effectiveness of anticoagulant therapies. Applicants respectfully traverse. The claims now all recite "human patient," and thus any disclosure of murine studies is not anticipatory. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. U.S. Patent 5,804,392

Claims 17-30 stand rejected as anticipated by the '392 patent. The claims, which are drawn to a method for identifying individuals in a hypercoagulable state, are allegedly presaged

by the statement, at column 4, lines 4-6 of the reference, that "levels of soluble EPCR appear to be correlated with inflammation and disease states associated with abnormal coagulation." The reference also discloses "Assays [for] measurement of soluble EPCR which are indicated of disease conditions involving coagulation ...." Applicants traverse, but in the interest of advancing the prosecution, these claims have been canceled without prejudice to filing of one or more continuing applications pursuing this subject matter. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejection Under 35 U.S.C. §103

Claims 2, 3 and 9-16 are rejected under §103 as obvious over Esmon in further view of Hirsh *et al.* Esmon is cited as above, and Hirsh is cited for teaching various anticoagulant therapies, and measuring the effectiveness of the anticoagulant therapy. Applicants traverse.

This cited passages from Esmon refer to the study by Gu *et al.* (2000) in which endotoxin or thrombin treatment elevated soluble EPCR levels in a rat experimental model. These are ***inflammatory*** mediators in sepsis, and the effect of thrombin was blocked by hirudin, a specific thrombin inhibitor. By way of discussing their results, both Gu *et al.* and Esmon extrapolated these observations in a rat model to the human condition by stating that monitoring plasma EPCR levels ***may*** indicate thrombin-mediated large vessel disease activity, and ***might*** prove useful to monitor disease progression or effectiveness of therapeutic interventions in these patients. It is agreed that endotoxin challenge and thrombin activity leads to production of soluble EPCR in rats.

However, the study described in Gu *et al.* (2000) was designed to investigate the mechanism by which soluble EPCR is generated using an *in vivo* model. It was not designed to

investigate how soluble EPCR levels change in patients as a result of anticoagulant therapy. Their data predicts that soluble EPCR levels may be linked to thrombin production in humans, but they do not test the prediction. They do not show data from patients or other humans in their study, which is precisely why the studies described in the present application were conducted.

The need for conducting studies in humans is at the crux of the rejection. The rejection is based on the assertion that observations on sEPCR levels in a rat experimental model are predictive of levels in the human condition. The scientific literature contains examples in which this is true, and others in which this prediction is ***not*** true. Thus, there is an inherent caveat absolutely required for interpretation of data collected in an animal model, namely, that such data are clearly representative of the animal model, but may not be representative of similar response in humans (or other animal models for that matter).

As one compelling example, the experiences of scientists and clinicians in the field of sepsis research have taught that this suspicion is absolutely valid. Over the past 15 years, use of compounds showing promising results in preliminary animal models were tested in randomized clinical trials in over 6,000 septic patients. The vast majority of these were disappointing failures and some actually increased mortality in patients (Redi *et al.* 1998; Vincent *et al.*, 2002). As an example, inhibition of pro-inflammatory cytokine TNFα in experimental animal models of sepsis dramatically improved mortality (Tracey *et al.*, 1987a,b; Fiedler *et al.*, 1992; Hinshaw *et al.*, 1990), but was ineffective in a large randomized clinical trial in septic patients (Abraham *et al.*, 1995). *Post hoc* analysis of clinical trials data sometimes identified patient sub-groups that may have responded to an intervention (Guiduci *et al.*, 1999), but the responses were very disappointing compared to that predicted from the dramatic effects observed in the earlier animal studies (Taylor *et al.*, 1988; Minnema *et al.*, 2000).

The reasons for these discrepancies are multi-dimensional and likely not solely due to the animal *vs.* human issue. Certainly, the complexity of consistent clinical diagnoses and patient stratification also contributes. However, some important pathways are known to be distinctly different between humans and especially rodents. One prominent example is the family of protease activated receptors (PARs), which bind thrombin and are activated by thrombin protease activity in a very distinct manner. There are several types of PARs, and these are differentially expressed in mice and humans. For example, thrombin signaling in mouse platelets is mediated by PAR-3 and PAR-4, whereas thrombin signaling in human platelets is mediated by PAR-1 and PAR-4 (Coughlin, 2001). Gu *et al.* (2000) demonstrated that thrombin was important for soluble EPCR generation in a rodent model, but thrombin receptors differ between rodents and humans. Thus, one must question whether thrombin would be important for soluble EPCR generation in humans based on the Gu *et al.* (2000) report alone.

Additionally, an experimental study typically is designed to limit confounding variables, so use of healthy in-bred rats of the same sex, age and weight are used, as was done by Gu *et al.* (2000). Experimentally, this is important because it is well accepted that certain experiments in rodents are not reproducible if performed in a different strain with a different genetic background. For example, sensitivity to bacterial toxin will vary widely between species of in-bred mice (Moayeri *et al.*, 2003). Humans, in contrast to in-bred animals, are a "messy" mix of genetics, gender, age and race, which is further complicated by multiple and overlapping disease processes that are rarely due to changes in one variable (*e.g.*, thrombin). Thus, even well-controlled animal studies can fall short in predicting clinical outcomes in humans.

Based on the foregoing explanation, it should be evident that is imperative to test predictions from animal models in humans, particularly in the field of inflammation. The data

provided in the instant application did precisely that, with both healthy human volunteers and patients with various cardiovascular diseases, using different anticoagulants with different mechanisms of action. These studies were specifically designed to test whether soluble EPCR levels reflect changes in thrombin generation due to therapeutic intervention in humans, and it was shown that soluble EPCR and F1+2 (a fragment released during prothrombin activation) levels decrease in response to anticoagulant intervention. Thus, by measuring sEPCR, one may monitor thrombin generation as a way of assessing the effectiveness of anticoagulant therapeutic intervention. However, without the data provided in the instant appliation, one of ordinary skill in the art would not have been able to predict whether the work done in rats was reasonably predictive of the human clinical situation.

Reconsideration and withdrawal of the rejection, based on the preceding discussion, is respectfully requested.

IV. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,

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